## REMARKS

Applicants wish to thank the Examiner for the Examiner's consideration given to this case to date.

## Status of Claims

The subject application was originally filed with 24 claims. On August 14, 2006, Applicants filed a First Preliminary Amendment, amending the subject application to add claims 25-33. On March 5, 2007, the Office issued a Restriction Requirement. On April 5, 2007, Applicants provisionally elected, with traverse in part, to prosecute claims 25-33. Applicants cancelled claims 15-24 without prejudice. Applicants traversed the restriction with respect to claims 1-14 and, in the May 9, 2007 Office Action, the Office rejoined claims 1-14. In Applicants' Amendment in Response to the May 9, 2007 Office Action, Applicants cancelled claims 5 and 12-14 without prejudice. In this Amendment, Applicants amend claims 1-4, 6-11, 25-28, 30, and 31 to present the claims in better form for consideration on appeal. Accordingly, claims 1-4, 6-11, and 25-33 remain pending in the subject application.

## Summary of Office Action

In the November 21, 2007 Office Action, the Office rejected claims 1-4, 6-11, 25, and 27-33 under 35 U.S.C. 103(a) as being unpatentable over Torchilin et al. (Biochim. Biophys. Acta 1996, 1279, 75-83) ("Torchilin") in view of Payne et al. (U.S. Patent No. 4,744,989) ("Payne") and further in view of Sachse et al. (Invest. Radiol. 1997, 32, 44-50) ("Sachse") or Leike et al. (Invest. Radiol. 2001, 36, 303-308) ("Leike"). Applicants note that no basis for rejection was given in the Office Action for claim 26, although Form PTOL-326 indicates that claim 26 stands rejected.

**Rejection of claims 1-4, 6-11, 25, and 27-33 under 35 U.S.C. § 103(a) as being unpatentable over Torchilin in view of Payne and further in view of Sachse or Leike.**

Amended claim 1 calls for liposomes which encapsulate one or more nonradioactive contrast-enhancing agents, the liposomes comprising cholesterol, at least one phospholipid, and at least one phospholipid which is derivatized with a polymer chain, wherein the liposomes are less than 150 nanometers in average diameter.

Amended claim 25 calls for liposomes comprising at least one first lipid or phospholipid; at least one second lipid or phospholipid which is derivatized with one or more polymers; and at least one sterically bulky excipient capable of stabilizing the liposomes; wherein the liposomes are less than 150 nanometers in average diameter, and wherein the liposomes encapsulate at least one nonradioactive contrast enhancing agent.

Both of amended claims 1 and 25 are directed to compositions "for enhancing contrast of one or more areas of a subject for X-ray imaging when administered to the subject."

As its principal reference, the Office cites Torchilin. Torchilin does not teach liposomes having a nonradioactive contrast enhancing agent encapsulated therein. Indeed, Torchilin does not teach a contrast enhancing agent at all. Torchilin is not silent on a tracing component, however. Rather, Torchilin affirmatively teaches a radioactive tracer—$In^{111}$, externally trans-chelated to DTPA. This is because Torchilin is not directed to enhancing contrast of one or more areas of a subject for X-ray imaging. A *prima facie* case of obviousness requires that "[a] prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." M.P.E.P. § 2141.02(VI). Accordingly, Applicants maintain their position that a person of ordinary skill in the art at the relevant time would have had no motivation to combine Torchilin with Payne, Sachse, or Leike.

As a secondary reference, the Office cites Payne. Payne discloses that the composition of the liposomes used is a key determinant of their size. While Payne purports to achieve the preparation of a "final liposome product of desired size, such as a mean diameter of within the range of from about 25 nm to about 12 μm" (col. 4, lines 54-58), Payne does not teach or even suggest a liposome having lipids or phospholipids which are derivatized with a polymer. In other words, Payne simply cannot be properly cited for teaching the manipulation of the size of liposomes comprising a lipid or phospholipid derivatized with a polymer and encapsulating a nonradioactive contrast enhancing agent.

Moreover, notwithstanding Payne's broad (and unsupported) statement regarding mean diameter, the examples of Payne almost exclusively demonstrate sizes of several microns. See, e.g., Examples 1 (5.3 μm), 2 (2.5 μm), 3 (5.3 μm), 4 (2.5 μm), and 7 (2.0 μm, 3.1 μm, and 4.25 μm). In Example 7, Payne refers to liposomes (composed of DMPC/DMPG/AmB) with "mean sizes of 100 to 150 nm," but those liposomes clearly: (1) are not polymer derivatized; (2) do not contain cholesterol; and (3) do not contain non-radioactive contrast enhancing agent. In short, the Office's implication that Payne teaches the ready manipulation of the size of relevant liposomes is incorrect.

The Office states: "The disclosures [of Torchilin and Payne] are drawn to the same products (liposomes) and the encapsulation of the contrast agents of Payne et al. into the liposomes of Torchilin et al. will have predictable results, as there are multiple factors for controlling the size of the liposomes." ¶ 13, p. 6.

Applicants respectfully suggest that the Office has grossly oversimplified the cited art and the subject application. Indeed, following the teachings of Payne, in combination with Torchilin, will not lead to the claimed invention. Moreover, the Office cannot simply ignore the plain teachings of Sachse, which post-dates Torchilin and Payne, when the Office dismisses the inventiveness of achieving the claimed compositions, having a mean diameter of less than 150 nm, as the result of "routine experimentation":

> Subsequently, surface-modification [of Iopromide-carrying liposomes] was performed by simple mixing with the respective PEG-derivative overnight. In the case of DSPE-PEG this procedure was accompanied by a ***drastic increase in vesicle size***. Thus, the resulting mean diameter amounted to 204 nm compared to 132 for the unmodified . . . .

Sachse, at p. 3 (emphasis added). Based on the teachings of Sachse (who is a person of extraordinary skill in the art), the achievement of the claimed liposome compositions—i.e., having both nonradioactive contrast enhancing agent and polymer-derivatized lipids or phospholipids, and having a mean diameter of less than 150 nm, is not obvious. To the contrary, Sachse represents solid evidence demonstrating a lack of expectation of success.

The Office further contends that: "It would be obvious to try/substitute the different lipids taught by Sachse et al. or Leike et al. for the lipids of the iodine agent containing/encapsulating liposomes of the combined disclosures of Payne et al. and Torchilin et al. as they are advantageous and suited for CT blood-pool imaging with iodinated contrast agents." ¶ 17, p. 7.

First, Leike does not teach phospholipids derivatized with polymer chains: "In the present study, tolerance, elimination, and diagnostic properties of ***unmodified*** (conventional) iopromide-carrying blood-pool liposomes were studied." Leike, p. 306 (emphasis added). Leike also does not teach liposomes having an average diameter of less than 150 nm. Leike, pp. 305 (201 nm). Thus, substitution of the lipids taught by Leike would not achieve the claimed invention. Second, the liposomes of Sachse, as described more fully above, also have a size greater than 200 nm, and, thus, their substitution would also not achieve the claimed invention. As described above, the combination of the disclosures of Payne and Torchilin, of which Sachse had the benefit, already has failed to prevent a "dramatic increase in size" upon Sachse's PEGylation of Sachse's 132 nm liposomes.

Finally, when positing what "would be obvious to try" regarding the various liposomes of the cited art for CT blood-pool imaging, the Office must consider the teachings representative of the state of the art in the relevant time period. For example, the Office must consider U.S. Patent No. 6,217,849 issued to Tournier et al., which post-dates Torchilin, Sachse, and Payne (Payne

was cited against Tournier). Tournier teaches vesicles in the 200 nm to 1 μm range, with an average diameter of 400 nm. Tournier, col. 4, lines 60-67. Tournier clearly teaches away from the use of the small liposomes of the subject application:

> The use of tiny liposome vesicles of the kind proposed in EP-A-0 442 962 for the delivery of drugs (in the order of 50 nm or less) ***are*** [sic] ***therefore unpractical for blood-pool imaging***. Much the same applies to the proposals of Gabison et al. in Biochim. Et Biophys. Acta 1103 (1992) 94-100 and I.A.J.M. Bakker-Woudenberg et al. ibid 318-326 directed to liposomes with an average size between 0.07 μm and 0.1 μm and prolonged residence times in the blood.

Tournier, col. 3, lines 14-22 (emphasis added). Tournier also teaches away from the use of polymer-derivatized liposomes. See col. 3, lines 30-35:

> ***[T]he production of liposomes with the "stealth factors" is rather cumbersome. In addition***, "stealth factored" liposomes are known to have very low entrapment capacity and while such liposomes may be suitable to carry specific drugs, and therefore useful in therapy, ***they are almost useless in imaging***.

Tournier, col. 3, lines 30-35 (emphasis added).

Thus, Tournier, another person of extraordinary skill in the art, had the benefit of the teachings of Torchilin, Sachse, and Payne, and still found stealth factors (i.e., polymer-derivatized lipids and phospholipids) to be "useless in imaging," and small liposomes to be "unpractical for blood pool imaging."

The teachings of Tournier are not counterbalanced by the Office's citation of Leike, as Leike expressly excluded polymer derivatized liposomes and liposomes having a mean diameter of less than 200 nm. Leike (2001) had the benefit of Tournier. Jens U. Leike is also an author of the Sachse publication, which was published prior to Tournier. Thus, if anything, Leike's express exclusion of polymer derivatized lipids and small liposomes in his second publication should be viewed as an adoption of Tournier's teachings against the use of stealth factors and small liposomes in imaging, further demonstrating an expectation of a lack of success at the relevant time period. Applicants respectfully note that the relevant time period for evaluating

what the person skilled in the pertinent art would have considered obvious is just prior to when the invention was made. 35 U.S.C. § 103(a).

Based on the foregoing, Applicants respectfully request that the Examiner withdraw the rejection of amended claim 1 and its directly or indirectly dependent claims 2-4 and 6-11, and amended independent claim 25 and its directly or indirectly dependent claims 26-33 under 35 U.S.C. § 103(a) as being unpatentable over Torchilin in view of Payne and further in view of Sachse or Leike.

## CONCLUSION

Applicants sincerely appreciate the Examiner's time and careful consideration of this submission. In view of the remarks above and the amendments presented herein, it is believed that claims 1-4, 6-11, and 25-33 are in condition for allowance and notice to such effect is respectfully requested. If the Examiner thinks another telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned at the phone number provided below.

If additional fees are due in connection with this Amendment, the Commissioner is authorized to charge Deposit Account No. 02-2051, identifying Docket No. 27428-4.

Respectfully submitted,

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